

Ex-2

# QUANTITATIVE COMPARISON OF TOXICITY OF ANTICANCER AGENTS IN MOUSE, RAT, HAMSTER, DOG, MONKEY, AND MAN<sup>1,2</sup>

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## SUMMARY

Toxicity data from small animals (mouse, rat, and hamster), large animals (dog and monkey), and humans were gathered, placed on a reasonably similar basis, and compared quantitatively. Each animal species and all species combined were used to predict the toxic doses in man (based on mg/m<sup>2</sup> of surface area). Two models were assumed for the relationship between the maximum tolerated dose (MTD) in man and the approximate LD10 in each animal system:

$$(\text{dose in man}) = (\text{dose in animal system } i) \quad (1)$$

and

$$(\text{dose in man}) = A_i \times (\text{dose in animal system } i), (i = 1, \dots, 6) \quad (2)$$

where  $A_i$  is the fraction of the dose in animals used to predict the dose in humans (assumed different for each animal system, ie,  $i = 1, \dots, 6$ ). It was found that when animal systems other than the rat were used the very simple model (1) was remarkably good for predicting the MTD in humans, though model (2) leads to slightly better predictions. Based on model (2), the animal systems are ranked in order of predictive ability: rhesus monkey, Swiss mouse, rat, BDF, mouse, dog, and hamster. The best estimate of the MTD in man is made by weighting the estimates from the various animal species. Dose on an mg/m<sup>2</sup> basis is approximately related to dose on an mg/kg basis by the formula

$$(\text{dose in mg/m}^2) = (km)_i \times (\text{dose in mg/kg}), (i = 1, \dots, 7)$$

where  $(km)_i$  is the appropriate factor for converting doses from mg/kg to mg/m<sup>2</sup> surface area for each species. When the  $(km)_i$  factors are known, equally good predictions of MTD in man can be made by either dose unit. On an mg/m<sup>2</sup> basis, the MTD in man is about the same as that in each animal species. On an mg/kg basis, the MTD in man is about  $\frac{1}{2}$  the LD10 in mice,  $\frac{1}{3}$  the LD10 in hamsters,  $\frac{1}{4}$  the LD10 in rats,  $\frac{1}{3}$  the MTD in rhesus monkeys, and  $\frac{1}{2}$  the MTD in dogs. In each case the ratio is the  $(km)$  factor in the animal system to that in man. Hence relationships among the various animal species and man are somewhat simpler and more direct on an mg/m<sup>2</sup> basis. These results support the conclusion that the experimental test systems used to evaluate the toxicities of potential anticancer drugs correlate remarkably closely with the results in man.

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The ~~long~~ aspect of a drug development program to discover compounds effective against any clinical disease is generally an exercise in comparative pharmacology. In the typical program, compounds are screened in small animals against some easily produced and reproduced pathologic condition. A close relationship must exist between the screening system and the ultimate clinical condition for the program to have the potential for success. Thus examination of this relationship is highly important. In cancer chemotherapy the similarities and differences have often been considered among transplantable tumors, virus-induced tumors, carcinogen-induced tumors, and spontaneous tumors in animals, and between animal tumors and the various cancers and leukemias in man. However the similarities and differences between mice, rats, hamsters, dogs, monkeys, and man have been considered less often in terms of quantitative and qualitative aspects of the toxic effects of drugs. The consistency of the action of therapeutic agents among various mammalian species is a keystone of most drug development programs, yet only rarely has this been studied in a quantitative manner.

Classically comparative pharmacology and physiology have been concerned with differences which permit analytic studies of specific biologic systems, and these studies have yielded valuable information. But it is equally important to consider the much more frequent similarities; we have tried to do this in the present analysis.

Of all the toxicologic end points, lethal toxicity is the easiest to measure with reasonable precision. Therefore we considered the lethal dose of certain cancer chemotherapeutic agents in various laboratory animals. For man the end point was the maximum tolerated dose (MTD). Hopefully two benefits might accrue from this evaluation: (1) If there is reasonable consistency in the reactions of various mammalian species, the toxicologic component of cancer chemotherapy screening will be shown to have a rational basis. (2) If such consistency is found, the problems of introducing highly toxic therapeutic agents into man might be approached more confidently. If major inconsistencies are discovered frequently, this would highlight the deficiencies in present screening systems and raise serious questions about the utility of these schemes for safe introduction of new drugs into man.

No attempt was made to relate therapeutic doses in the various mammalian species. In future this correlation should be attempted since the therapeutic target in the host is the same as the toxicity target. However if an agent has therapeutic properties in an experimental system, it is well to know the dose levels for patients. Since there is some justification for using MTD's in cancer therapy, these levels were studied.

The plan of this retrospective study was to examine considerable toxicologic data obtained in (a) small animals, used in primary screening and quantitative secondary drug evaluation; (b) larger animals, dogs and monkeys, the quantitative and qualitative aspects of toxicity at sublethal and lethal levels; and (c) man, the target species. The goal was to determine what relationship exists, if any, between certain commonly used toxicologic end points in the various animal species and man for a number of anticancer agents.

Nothing in this report is intended to suggest or imply that short cuts are allowable in clinical or pre-clinical toxicologic studies. Dose limiting and serious toxic effects in man are always apparent from even the most carefully done toxicologic investigations in animals. It is emphasized and should be clearly understood that it is dangerous to attempt to extrapolate directly from animal toxicity data to maximum tolerated doses in man! New drugs can be introduced safely into clinical trial only through careful toxicologic and pharmacologic study in animals and then very cautious study in man, starting with much lower doses than those which appear to be tolerated by animals.

#### APPROACHES AND ASSUMPTIONS IN THIS STUDY

The published and unpublished data which form the basis for this analysis were obtained by numerous investigators using different protocols and end points. We used consistent reasonable general assumptions so that the data were comparable. The biologic end points, protocols, assumptions, and corrections necessary to make the results more comparable are described briefly.

#### Toxicologic End Points (See Appendix I)

Mouse, rat, or hamster: Lethality—the dose which when administered by a certain route and schedule killed a selected percentage (10%, i.e. the LD10) during a specified observation period; 50 to more than 100 animals were used in a typical determination.

Dog or monkey: (a) MTD; typically 2-4 animals were used at each dose level, spaced by 2-fold increments. In all instances individual doses which killed 0 and 100% were used. The highest dose killing 0% was considered the MTD. (b) Dose-related, hematopoietic effects; localized hemorrhages of the gastrointestinal tract; generalized hemorrhagic lesions (abdominal and thoracic viscera); stimulation of the central nervous system (CNS); others.

Man: (a) MTD for a fixed schedule (dose causing mild to moderate sublethal toxic effects in a significant percent of patients); (b) MTD for a variable schedule, calculated from the daily dose and median period to toxic effects requiring cessation of drug; the judgment of many clinical investigators was necessarily accepted in making this estimation.

Because of the nature of the available data, the toxicologic end points in the various animal species were related to the MTD in man. Although it was necessary to assume that the dosages resulted in the same percentage of toxicity in each species, the results do not depend in a major way, on this assumption. For the drugs in this study, the dose-toxicity curves were relatively steep so that if the true percentage of toxicity for a given dosage was, say, between 5% and 15%, the actual dosage used would not differ very much from the dosage that should have been used.

It was necessary to use toxicologic data obtained by various routes of drug administration, ie, intraperitoneal (ip) for small animals, oral for small animals and man, and intravenous (iv) for large animals and man. In mice and rats the LD10's obtained by the ip and iv routes are usually comparable.

Another variable for which some reasonable correction must be made is the dosage schedule including the total dose. We assumed that the toxicity of anticancer agents is cumulative. Griswold et al. (3) reported that when the LD10's in BDF, mice of 70 agents, including the major classes of anticancer agents, were compared for two schedules, qd 1-7 days and qd 1-11 days, the mean ratio (qd 1-7 days/qd 1-11 days) was 1.56. This is very close to that which might be expected from direct cumulative drug toxicity (11 days/7 days = 1.57).

Pinkel (2) and other investigators pointed out that the usual doses of certain drugs in various animal species and man were comparable when the dose was measured on the basis of  $\text{mg}/\text{m}^2$  of surface area. Consequently most of the results are presented in  $\text{mg}/\text{m}^2$ . However since  $\text{mg}/\text{kg}$  is a commonly used unit of drug dosage, some results are also presented in this

unit. Only a simple transformation is required to change  $\text{mg}/\text{kg}$  to  $\text{mg}/\text{m}^2$ ; therefore the relationships developed are equivalent whichever unit is used. The quantitative relationships were simpler when expressed in  $\text{mg}/\text{m}^2$ .

A conversion factor ( $km$ ) was used to transform  $\text{mg}/\text{kg}$  to  $\text{mg}/\text{m}^2$  by the equation  $\text{mg}/\text{kg} \times (km) = \text{mg}/\text{m}^2$ ; ( $km$ ) factors for animals, given their weight, are presented in table 1 (Appendix II), and table 2 (Appendix II) presents a way of transforming doses in  $\text{mg}/\text{kg}$  to  $\text{mg}/\text{m}^2$  for man, given height and body weight. Chart 1 (Appendix II) is a diagram for determining surface area in man, given height and weight.

Calculations based on units of body surface area have no intrinsic merit per se. Very likely some other basis such as surface area of the site of action of the drug, lean body mass, or some fractional power of body weight, possibly related to length or some organ-membrane surface area, would be as appropriate or more appropriate. However the body surface area has been used to relate many physiologic parameters among species and means of transforming the data are readily available. Further, in our clinical studies we routinely use body surface area to adjust drug dose for patients of different size and weight.

## RESULTS

The first step in analyzing the data was to correct the daily dosage schedules for man and for animals, when necessary, to a uniform schedule of qd 1-5 days. Thus if an LD10 for mice, or MTD for man, was obtained by a schedule of qd 1-10 days, we calculated that the LD10 (or MTD) for a schedule of qd 1-5 days was twice that value. The next step was to convert doses (LD10's or MTD's) from  $\text{mg}/\text{kg}$  to  $\text{mg}/\text{m}^2$ . This was accomplished by the approximate formula

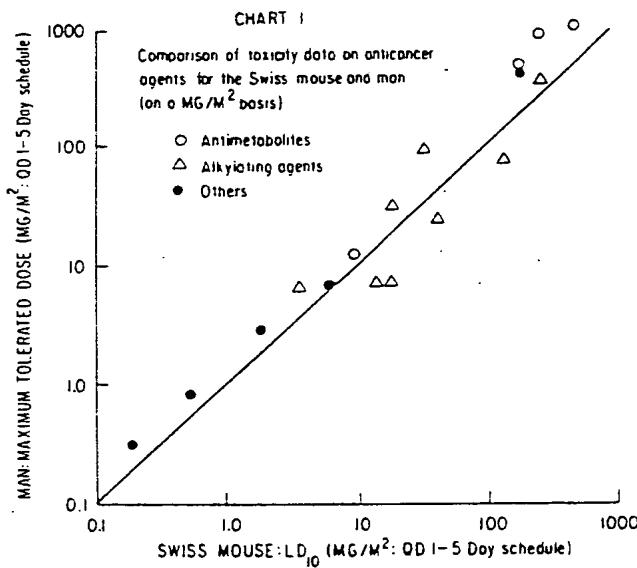
$$(\text{mg}/\text{m}^2) = (km)_i \times (\text{mg}/\text{kg}), (i=1, \dots, 7)$$

where the  $(km)_i$  factor differs according to the species and also according to body weight within each species. In the analysis an average  $(km)_i$  factor was used, assuming that individuals in each species were of average height-to-body-weight ratios. The  $(km)_i$  factors were derived from standard relationships between weight and surface area as given in Spector (40) and Sendroy and Cecchini (39). Details and other information on relating drug doses in  $\text{mg}/\text{kg}$  to doses in  $\text{mg}/\text{m}^2$  are given in Appendix II.

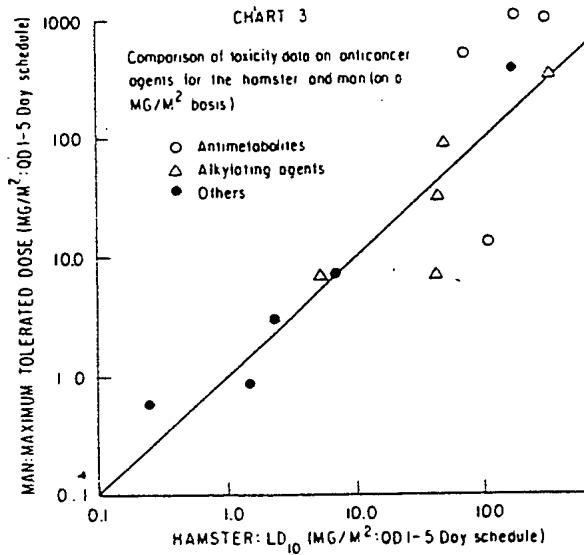
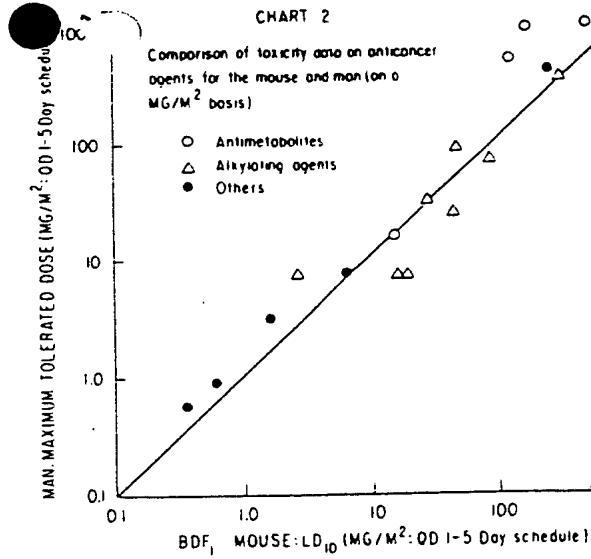
\*qd = drug given once daily for as many days as indicated.

The drugs used in this study are given in table 1. Doses of 18 drugs are presented in mg/kg and mg/m<sup>2</sup> for the 6 species, along with source information and other pertinent data. An average dose (LD<sub>10</sub> or MTD) of each drug was calculated from the multiple studies, if done, on each species. The average doses for the 6 animal systems and man are given in mg/kg in table 2, and in mg/m<sup>2</sup> in table 3. Charts 1-6 indicate the closeness of the relationship between the logarithm of the LD<sub>10</sub>, or MTD, in the various animal systems and in man when the dose is measured in mg/m<sup>2</sup>. Chart 7 indicates the close relationship between 12 times the LD<sub>10</sub> in the BDF, mouse and the MTD in man when the dose is measured in mg/kg. The ratio of the (km) factors for an average man and a mouse is 37/3 = 12.3. It will be shown later that relationships between systems on an mg/kg basis are the same as those on an mg/m<sup>2</sup> basis if the ratio of (km) factors is considered.

To examine further the relationship of dosage, in mg/m<sup>2</sup>, between the animal systems and man, consider the following: For each animal system and man, there is a dose-toxicity curve. The basic data for each drug consist of estimates of a single point, the approximate LD<sub>10</sub>, on the dose-toxicity curves for man and the 6



\*Chemical Abstracts' nomenclature and NSC numbers for the agents are given on page 243.



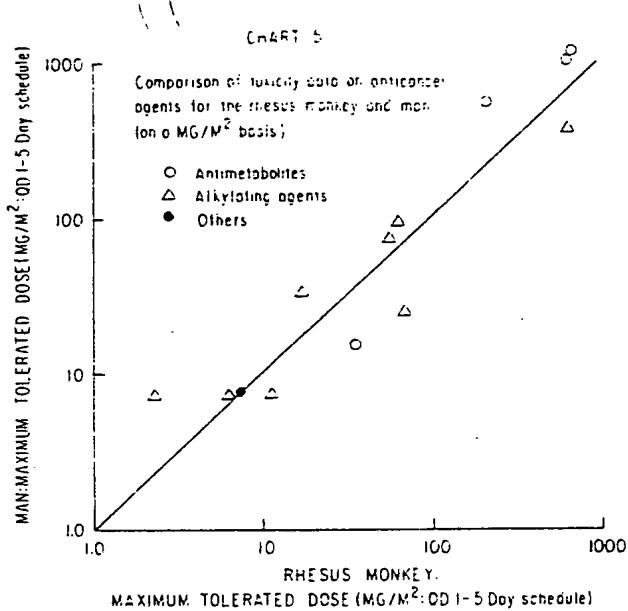
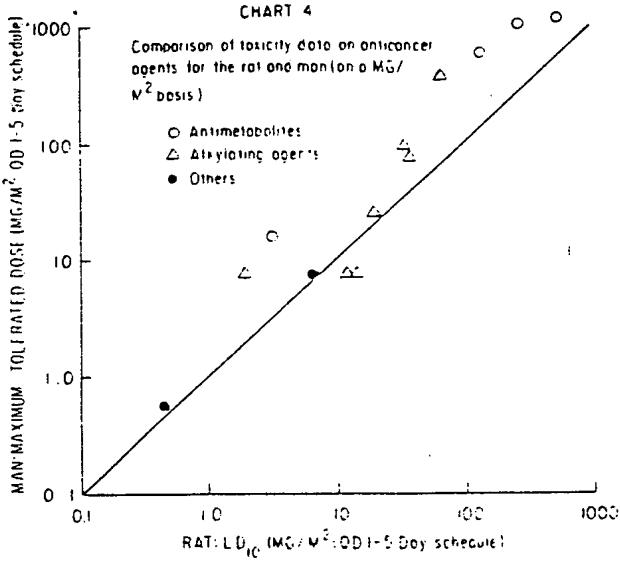
animal systems. We wish to describe the relationship between the dose-toxicity curve for man and that for each of the animal systems. Two models are considered:

$$(\text{dose in man}) = (\text{dose in animal system } i) \quad (i = 1, \dots, 6)$$

and

$$(\text{dose in man}) = A_i \times (\text{dose in animal system } i), \quad (i = 1, \dots, 6).$$

Model (1) is a special case of model (2) since they are the same when  $A_i = 1$ . M

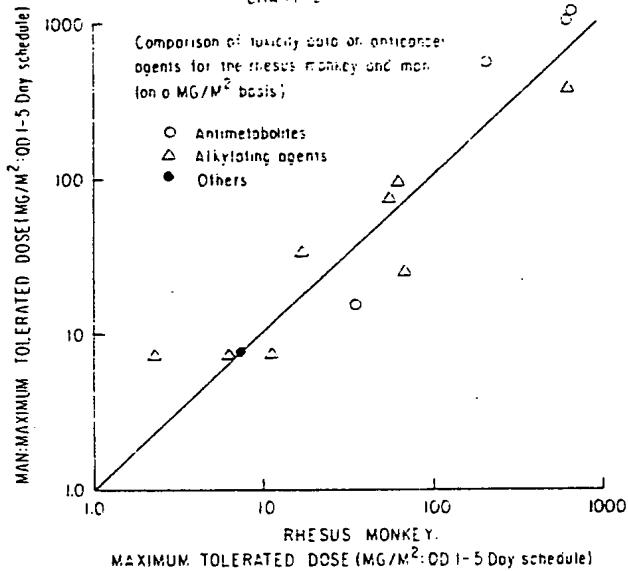
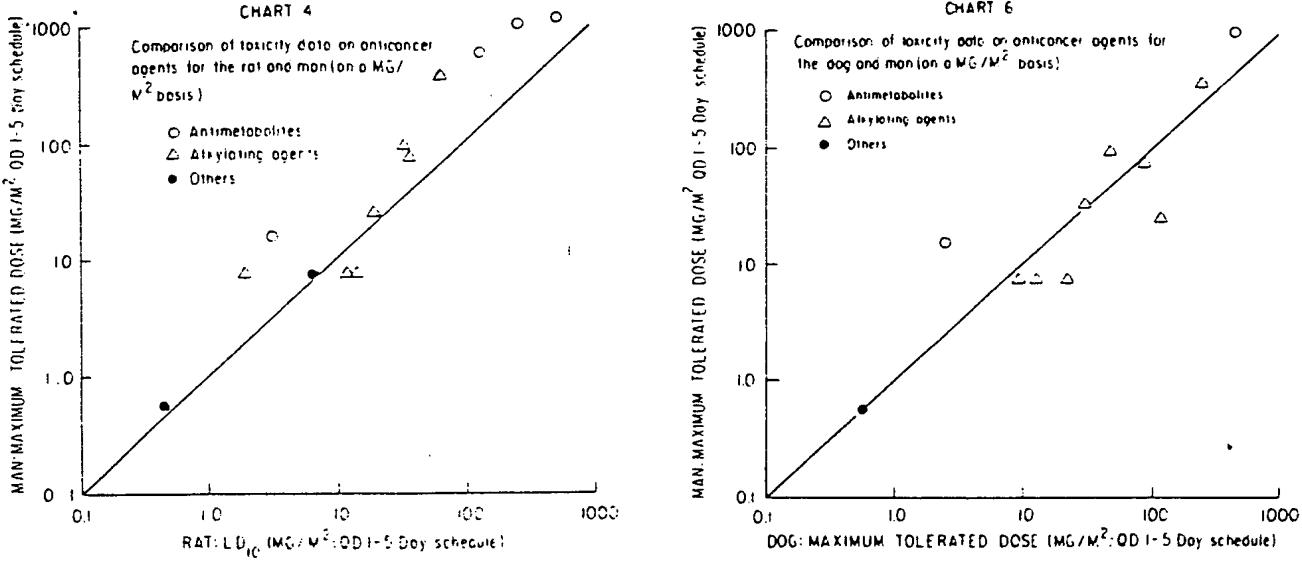


(1) assumes that the dose in each animal system gives a direct prediction of the dose in man. Model (2) assumes that the dose in man is a fraction ( $A_i$ ) of the dose in the animal system and the fraction remains constant for the sample of drugs.

A third model was considered:

$$(\text{dose in man}) = A_i \times (\text{dose in animal system } i)^{B_i}, \quad (i = 1, \dots, 6)$$

where  $B_i$  is the power to which the dose is



raised, assumed to be 1 in models (1) and (2). This model is a natural generalization of (2). However, since the estimates of  $B_i$  were near 1 for all animal systems, in fact within 1 standard error (SE) limit, there is no advantage to using a more general model than (2).

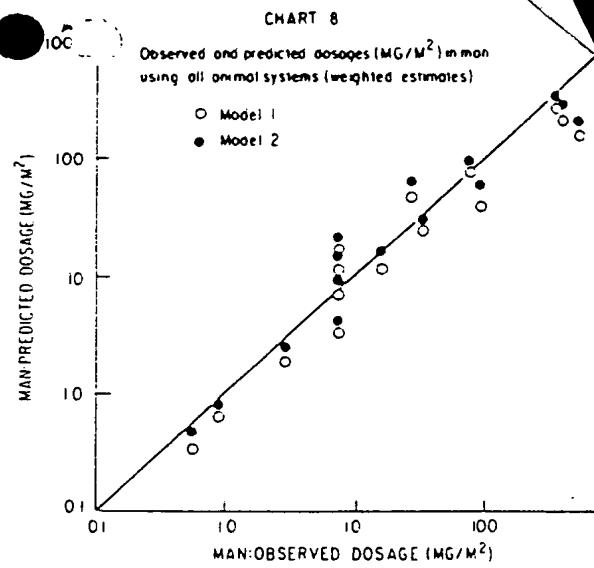
By these models, we wish to predict the dose in man from the dose in each animal system when both determinations are subject to sampling variation (and other assumptions as men-

tioned) in the sample of drugs. The statistical considerations in fitting these models are given in Appendix III.

Model (1) is the simplest possible model; no parameters need to be estimated. Thus the doses in table 3 for each animal system are the predicted values of the dose in man and charts 1-6 indicate that these predictions are reasonably good. The standard deviations, on a log scale, of a predicted value of log (dose in man) were calculated for each animal system. The systems are ranked in order of predictive ability in the top half of table 4: monkey, Swiss mice, BDF, mouse, dog, rat, and hamster. A predicted value of the dose in man has been calculated by weighting the estimates from each animal system (see Appendix III) and the results are given in the last column of table 3. The standard deviation of a predicted value of log (dose in man) is 0.299, with multipliers of 0.50 and 2.0 for lower and upper standard deviation limits respectively. Thus the weighted estimate based on all systems is better than the estimate from any single system.

Assuming model (2), the estimates of  $A_1$  and  $A_2 \pm 2 \text{ SE}$  are given in the bottom half of table 4. Note that the approximate 95% confidence limits for the multiplying factor,  $A_1$ , include 1 for all animal systems except the rat. Thus for the other animal systems it is reasonable to accept the very simple model (1) as providing an adequate prediction of the dose in man. However when all systems are combined to obtain an overall estimate of  $A_1$  (see Appendix III), the approximate 95% confidence limits do not include 1. Also, note from the bottom half of table 4 that the standard deviation of a predicted value of log (dose in man) is 0.275, almost a 10% reduction from that of model (1). Therefore model (2) is preferred for fitting these data; however for future studies in which more precise estimates of LD<sub>10</sub> are available, it may be that model (1) will be adequate.

Using model (2), we can rank the animal systems in order of their predictive ability by considering the deviations of observed from predicted values of dose in man. These standard deviations are given in table 4. Thus the order is monkey, Swiss mouse, rat, BDF, mouse, dog, and hamster. The best predictions with model (2) are obtained by weighting the estimates of the dose in man from all 6 animal systems (the method is explained in Appendix III). The predictions for the drugs in this study are given



in table 5 and the weighted estimates based on all animal systems combined are plotted in chart 8. The best estimates of dose in man, indicated by the standard deviations in table 4, are given by weighting the individual estimates from each animal system.

Another model was considered in which the dose in man (mg/m<sup>2</sup>) was related to doses in the animal species in a single equation:

$$\begin{aligned}
 \log(\text{dose in man}) = & 0.284 + 0.847 \log(\text{dose in Swiss mouse}) \\
 & - 1.064 \log(\text{dose in BDF mouse}) \\
 & + 0.539 \log(\text{dose in rat}) \\
 & + 0.801 \log(\text{dose in monkey}) \\
 & - 0.175 \log(\text{dose in dog})
 \end{aligned}$$

This predicting equation leads to a slight improvement in the prediction of the dose in man. The deviations of observed from predicted dosages were less (standard deviation of 0.249 on a log scale compared to 0.275 by using weighted combined estimates). However a prediction of dosage in man cannot be made unless estimates of LD<sub>10</sub> are available from all the animal systems mentioned; also the model does not provide any real insight into the relationship between the dose-toxicity curve in each animal system and that in man.

From considering charts 1-6, this question arose: Do the differences between the do-

toxicity curves for man and for each animal system differ depending on whether an antimetabolite or an alkylating agent was given? Usually the animal species, except the rat and monkey, underpredict the doses of antimetabolites and overpredict the doses of alkylating agents for man. By a statistical test (t test), there was some suggestion ( $P < 0.10$ ) that in Swiss mice and BDF, mice the predictions of dosage in man were lower for antimetabolites than for alkylating agents. There was no evidence of a difference in the other species. Only 4 antimetabolites and 8 alkylating agents were tested in all animal species. Consequently further study is needed to determine whether the difference between dose-toxicity curves really depends on the type of agent.

There is some value in comparing the relationships found on an  $\text{mg}/\text{m}^2$  basis with what would have been found on an  $\text{mg}/\text{kg}$  basis. Some indication of this has already been given in chart 7 which shows that there is a close relationship between 12 times the LD10 in the BDF, mouse and the MTD in man. Since the relationship between  $\text{mg}/\text{kg}$  and  $\text{mg}/\text{m}^2$  used is  $(\text{mg}/\text{m}^2) = (km)_i \times (\text{mg}/\text{kg})$ , ( $i = 1, \dots, 7$ ), models (1) and (2) become, in terms of  $\text{mg}/\text{kg}$ ,

$$(\text{dose in man}) = \frac{(km)_i}{(km)_m} \times (\text{dose in animal system}) \quad (1)$$

and

$$(\text{dose in man}) = \frac{(km)_i}{(km)_m} A_i \times (\text{dose in animal system}) \quad (2)$$

where  $(km)_i$  and  $(km)_m$  refer to the  $(km)$  factor in the particular animal system and man respectively, and  $A_i$  is exactly the same as stated before. Hence it should be clear that dose in man can be predicted equally well either on an  $\text{mg}/\text{kg}$  basis or on an  $\text{mg}/\text{m}^2$  basis. Thus by using the  $km$  factors and model (1), the dose in man ( $\text{mg}/\text{kg}$ ) is approximately  $\frac{1}{2}$  the dose in mice,  $\frac{1}{6}$  the dose in hamsters,  $\frac{1}{4}$  the dose in rats,  $\frac{1}{3}$  the dose in rhesus monkeys, and  $\frac{1}{2}$  the dose in dogs.

#### DISCUSSION

Originality is not claimed or implied for this analysis. We have confirmed and extended the general observations and conclusions of

Pinkel (2) who confirmed and extended specific aspects of the basic observation of Rubner (36), made 80 years ago, and many other investigators later.

The availability of much more extensive toxicity data from the Cancer Chemotherapy National Service Center program, from certain other published sources, and from our own laboratories seemed to make this present analysis timely. Also we believe it is important to use more definitive biologic end points of toxicity. This analysis and study of data on toxicity to animals and humans of several types of anticancer agents (tables 1, 3, and 5) lead us to conclude that the toxic dose of an agent is similar among species when the dose is measured on the basis of surface area. The skin surface area was used here though it is unlikely that the skin is the target area of action of any particular drug. More likely the skin surface is more or less proportional to the true target surface.

To the extent that mammalian species are broadly similar and have corresponding organs and tissues, it is true that any surface area will increase approximately with the two-thirds power of weight (38). Thus the two-thirds power of body weight would have been a convenient unit of surface area to use and the results of the analysis would have been almost the same (see Appendix II).

Pinkel (2) suggested that "cancer chemotherapists consider the applicability of body surface area as a criterion of drug dosages in their laboratory and clinical studies." We suggest that a unit proportional to body surface area is sufficient and an appropriate unit is  $(\text{weight})^{2/3}$ .

We have been concerned only with comparisons among species, not within species, and with adult animals, not immature and adult animals. Also we have been concerned solely with anticancer drugs.

Some of the toxicologic data tabulated may disagree with unpublished and published observations of some experimentalists and clinicians. The Acute Leukemia Task Force of the National Cancer Institute wishes to correct, update, and extend this analysis at some future time. Those interested in seeing such correlation efforts extended can help by providing ad-

ditional data, such clinical and experimental, in a form similar to that in table 1.

The present study has emphasized the quantitative aspects of toxicity of anticancer drugs to animals and man. Regarding the prediction of the qualitative effects of anticancer drugs in man from laboratory animal studies, Owens (1) suggested:

| <i>Predictive value</i> | <i>Preclinical toxicity studies</i>  |
|-------------------------|--|
| Good                    | Bone marrow, gastrointestinal tract, liver, kidney                                     |
| Questionable            | Nervous system, including peripheral neuropathy, extraocular palsies, and CNS toxicity |
| None                    | Skin and appendages, including skin rashes, dermatitis, and alopecia                   |

Of the 18 agents in this study, 17 produced limiting toxicity to the bone marrow (marrow depression: MD) and to the gastrointestinal (GI) tract. If the  $\text{mg}/\text{m}^2$  doses in man that are predicted by using the weighted combined estimate are compared to the observed doses, then the largest ratio of predicted dose/observed dose is 3, for thioTEPA. Consequently it would be reasonable to study preclinical toxic effects in the mouse, rat, dog, monkey, and hamster, to estimate the MTD ( $\text{mg}/\text{m}^2$ ) in man, and to start clinical cancer chemotherapy trials at about one-third the predicted dose. This would have been a safe procedure for all 18 drugs mentioned. Owens (1) suggested that it might be reasonable "to begin a human trial at one-tenth of the maximum tolerated dose in the most susceptible animal" (on an  $\text{mg}/\text{kg}$  basis). Since the most susceptible animal will ordinarily be the dog or rhesus monkey, Owens' rule of thumb on an  $\text{mg}/\text{m}^2$  basis becomes: begin trial in man at about one-third the dose for monkeys or one-fifth the dose for dogs. Thus there is reasonable agreement between the two recommendations. However if the ani-

mal is not placed on the  $\text{mg}/\text{m}^2$  basis before using Owens' rule of thumb, any additional knowledge which the small animal (mouse and rat) might contribute will be overlooked. Remember also that the toxicity values (LD10's) for such small animals are often more reliable statistically because more animals are generally used.

The ratios of animal/human toxicity ( $\text{mg}/\text{m}^2$  basis) for the mouse, hamster, dog, and monkey are remarkably close to unity. Thus each species generally predicts for man. That this is true for the mouse is particularly pertinent to cancer chemotherapy. Extensive drug development programs which use mouse tumors seem to be on firmer ground than we had previously thought. In general the rat is more susceptible to these agents than the other species. The hamster is unusually resistant to amethopterin and sensitive to the fluorinated pyrimidines. The dog and monkey, long known to be reasonably good predictors of toxicity to humans, have shown up well in this analysis.

We are not suggesting that it is wise to use mouse or rat LD10's, convert the doses to  $\text{mg}/\text{m}^2$ , and then start clinical trials at one-third this level (in  $\text{mg}/\text{m}^2$  for man). The additional safety provided by toxicity data from multiple species is well established, as is the value of specific qualitative knowledge on drug related sublethal toxicity and its reversibility.

Finally it is suggested that the quantitative relationships between toxicity to animals and to humans are simpler when compared on a  $\text{mg}/\text{m}^2$  basis than on an  $\text{mg}/\text{kg}$  basis. Broad use of a surface area unit, either  $\text{mg}/\text{m}^2$  or  $(\text{weight})^{0.75}$ , by experimental and clinical cancer chemotherapists, as well as biochemists and pharmacologists concerned with mechanistic studies, might prove helpful in many types of experimental planning and data analysis.

Topic 1

Comparison of Approximate Maximum Human Doses of Certain Antiseptics. Areas with 10% for the 10% Rat, and Hamster and Approximate Maximum Nonethiob Dose for the Dog and Monkey

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Tome 1 (Cont'd.)

Table 1 (Cont'd.)

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Table I (Cont'd)

| Agent             | Species (a) | No. of Patients or Animals | Drug Administration Schedule (days) | Route            | Period of Observations |                  |      | Toxicologic End Point for Species Indicated |                  |                    | Brief Toxicity Rating in Men: and Intensity of Major Reactions in Large Animals |                  |                  | Limiting Toxicologic Symptoms or Severity |                  |                  | Daily Dose (qd 1-5 days) |                  |                  |        |
|-------------------|-------------|----------------------------|-------------------------------------|------------------|------------------------|------------------|------|---|------------------|--------------------|---|------------------|------------------|---|------------------|------------------|--------------------------|------------------|------------------|--------|
|                   |             |                            |                                     |                  | 1                      | 2                | 3    | MTD   | OS               | 35%                | CI: MD  | CI: MD           | CI: MD           | CI: MD                                    | CI: MD           | CI: MD           | CI: MD                   | CI: MD           | CI: MD           | CI: MD |
| 13. Actinomycin D | Man         | 25                         | I.V. qd 1-3                         | I.V. qd 1-3      | 1-31                   | 1-31             | 1-31 | MTD   | OS               | 35%                | 30%   | 15%              | CI: MD           | 0.013                                     | 0.013            | 31.0             | 0.33*                    | 31.0             | 0.33*            | 31.0   |
|                   | Swiss mouse | 50-100                     | I.P. qd 1-5                         | I.P. qd 1-5      | 1-21                   | 1-21             | 1-21 | LD <sub>50</sub>                            | LD <sub>50</sub> | LD <sub>50</sub>   | LD <sub>50</sub>  | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>                          | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>         | LD <sub>50</sub> | LD <sub>50</sub> |        |
|                   | UDF mouse   | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-21                   | 1-21             | 1-21 | LD <sub>50</sub>                            | LD <sub>50</sub> | LD <sub>50</sub>   | LD <sub>50</sub>  | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>                          | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>         | LD <sub>50</sub> | LD <sub>50</sub> |        |
|                   | Swiss mouse | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-21                   | 1-21             | 1-21 | LD <sub>50</sub>                            | LD <sub>50</sub> | LD <sub>50</sub>   | LD <sub>50</sub>  | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>                          | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>         | LD <sub>50</sub> | LD <sub>50</sub> |        |
|                   | UDF mouse   | 50-100                     | I.P. qd 1-11                        | I.P. qd 1-11     | 1-21                   | 1-21             | 1-21 | LD <sub>50</sub>                            | LD <sub>50</sub> | LD <sub>50</sub>   | LD <sub>50</sub>  | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>                          | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>         | LD <sub>50</sub> | LD <sub>50</sub> |        |
|                   | Hamster     | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | 1-14             | 1-14 | LD <sub>50</sub>                            | LD <sub>50</sub> | LD <sub>50</sub>   | LD <sub>50</sub>  | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>                          | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>         | LD <sub>50</sub> | LD <sub>50</sub> |        |
|                   | H. Rat      | 50-100                     | I.P. qd 1-5                         | I.P. qd 1-5      | 1-21                   | 1-21             | 1-21 | LD <sub>50</sub>                            | LD <sub>50</sub> | LD <sub>50</sub>   | LD <sub>50</sub>  | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>                          | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>         | LD <sub>50</sub> | LD <sub>50</sub> |        |
|                   | F. Rat      | 50-100                     | I.P. qd 1-5                         | I.P. qd 1-5      | 1-21                   | 1-21             | 1-21 | LD <sub>50</sub>                            | LD <sub>50</sub> | LD <sub>50</sub>   | LD <sub>50</sub>  | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>                          | LD <sub>50</sub> | LD <sub>50</sub> | LD <sub>50</sub>         | LD <sub>50</sub> | LD <sub>50</sub> |        |
|                   | Dog         |                            | I.V. qd 1-15                        |                  |                        |                  |      | MTD   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
| 14. Mitomycin C   | Man         | 12                         | I.V. qd 1-4 (b)                     | I.V. qd 1-6 (b)  | 21                     | MTD              | 1    | 1   | 7                | 3                  | MD  | 0.13             | 0.13             | 0.10                                      | 0.10             | 0.10             | 0.10                     | 0.10             | 0.10             | 0.10   |
|                   | Swiss mouse | 50                         | I.V. qd 1-10                        | I.V. qd 1-10     | 13                     | MTD              | 10%  | 45%   | 5%               | MD                 | 0.10  | 0.10             | 0.10             | 0.10                                      | 0.10             | 0.10             | 0.10                     | 0.10             | 0.10             | 0.10   |
|                   | UDF mouse   | 50-100                     | I.P. qd 1-5                         | I.P. qd 1-5      | 1-21                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Swiss mouse | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | UDF mouse   | 50-100                     | I.P. qd 1-11                        | I.P. qd 1-11     | 1-21                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Hamster     | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | H. Rat      | 50-100                     | I.P. qd 1-5                         | I.P. qd 1-5      | 1-21                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | F. Rat      | 50-100                     | I.P. qd 1-5                         | I.P. qd 1-5      | 1-21                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Monkey      | 6                          | I.V. qd 1-2                         | I.V. qd 1-2      | 1-30                   | MTD              | CI   | MD  | CI               | MD                 | CI  | MD               | CI               | MD  | CI               | MD               | CI                       | MD               | CI               | MD     |
| 15. Vinblastine   | Man         | 20                         | I.V. qd 1-3                         | I.V. qd 1-3      | 10-14                  | MTD              | 1%   | 10%   | 30%              | ALD                | 0.13  | 0.13             | 0.10             | 0.10                                      | 0.10             | 0.10             | 0.10                     | 0.10             | 0.10             | 0.10   |
|                   | Swiss mouse | 10                         | I.V. qd 1-3                         | I.V. qd 1-3      | 10-14                  | MTD              | 0    | 1   | 4                | MD                 | 0.10  | 0.10             | 0.10             | 0.10                                      | 0.10             | 0.10             | 0.10                     | 0.10             | 0.10             | 0.10   |
|                   | 21          | I.V. qd 1-5                | I.V. qd 1-5                         | 10-14            | MTD                    | 0                | 6    | 1   | B (partial) MD   | 0.10               | 0.10  | 0.10             | 0.10             | 0.10                                      | 0.10             | 0.10             | 0.10                     | 0.10             | 0.10             |        |
|                   |             | (2-7)                      |                                     |                  |                        |                  |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Swiss mouse | 50-100                     | I.V. once wk & 1                    | I.V. once wk & 1 | 1-30                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Swiss mouse | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | UDF mouse   | 50-100                     | I.P. qd 1-11                        | I.P. qd 1-11     | 1-21                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Hamster     | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   |             | 28                         | I.V. once wk & 1                    | I.V. once wk & 1 | 1-21                   | MTD              | OS   | 10%   | 30%              | 40%                | Per cent, max. & 1  | 0.02             | 0.02             | 0.02                                      | 0.02             | 0.02             | 0.02                     | 0.02             | 0.02             | 0.02   |
|                   | 10          | I.V. qd 1-4 (a)            | I.V. qd 1-4 (a)                     | 1-21             | MTD                    | OS               | 10%  | 30%   | 40%              | Per cent, max. & 1 | 0.03  | 0.03             | 0.03             | 0.03                                      | 0.03             | 0.03             | 0.03                     | 0.03             | 0.03             | 0.03   |
|                   |             |                            |                                     |                  |                        |                  |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
| 16. Vinorelbine   | Man         | 10                         | I.V. qd 1-4 (a)                     | I.V. qd 1-4 (a)  | 1-21                   | MTD              | OS   | 10%   | 30%              | 40%                | Per cent, max. & 1  | 0.03             | 0.03             | 0.03                                      | 0.03             | 0.03             | 0.03                     | 0.03             | 0.03             | 0.03   |
|                   |             |                            |                                     |                  |                        |                  |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Swiss mouse | 50-100                     | I.P. once wk & 1                    | I.P. once wk & 1 | 1-20                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Swiss mouse | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | UDF mouse   | 50-100                     | I.P. qd 1-11                        | I.P. qd 1-11     | 1-21                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Hamster     | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
| 17. Methyl GTO    | Man         | 36                         | I.V. qd 1-14 (b)                    | I.V. qd 1-14 (b) | 10-21                  | MTD              | (55) | (20%)                                       | (5%)             | (30%)              | (11%)   | skin             | 1                | 1   | 1                | 1                | 1                        | 1                | 1                | 1      |
|                   |             | 12                         | I.V. qd 1-11 (b)                    | I.V. qd 1-11 (b) | 10-14                  | MTD              | (55) | (20%)                                       | (5%)             | (30%)              | (11%)   | skin             | 3.0              | 3.0                                       | 3.0              | 3.0              | 3.0                      | 3.0              | 3.0              | 3.0    |
|                   | Swiss mouse | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | UDF mouse   | 50-100                     | I.P. qd 1-11                        | I.P. qd 1-11     | 1-21                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   | Hamster     | 50-100                     | I.P. qd 1-7                         | I.P. qd 1-7      | 1-14                   | LD <sub>50</sub> |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   |             | 16                         | Once wk & 1                         | Once wk & 1      | 3-28                   | MTD              | OS   | 10%   | 10%              | 10%                | 10%   | 10%              | 50.0             | 50.0                                      | 50.0             | 50.0             | 50.0                     | 50.0             | 50.0             |        |
|                   | 9           | Once                       | qd 1-10 (b)                         | Once             | qd 1-10 (b)            | 3-28             | MTD  | OS  | 10%              | 10%                | 10%   | 10%              | 10%              | 60.0                                      | 60.0             | 60.0             | 60.0                     | 60.0             | 60.0             | 60.0   |
|                   |             |                            |                                     |                  |                        |                  |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
| 18. Hydroxyurea   | Man         |                            |                                     |                  |                        |                  |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   |             |                            |                                     |                  |                        |                  |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   |             |                            |                                     |                  |                        |                  |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |
|                   |             |                            |                                     |                  |                        |                  |      |   |                  |                    |   |                  |                  |   |                  |                  |                          |                  |                  |        |

(Continued)

Table I (Cont'd)

Note. (a) All of the human toxicity data are calculated on the basis of a 60-kg man (kin factor = 3); approximately 20-gram mice were employed; 50-gram hamsters; 100-gram rats (except where otherwise indicated); 2.5-kg (Rhesus monkeys); 7 to 8-kg Young Beagle dogs (7-12 months of age).

(b) Numbers of patients exhibiting the indicated degree of "toxicity" are given unless the value is indicated as per cent. The intensity of nausea, depression and gastrointestinal toxicity based on the average or most frequent observed for dogs or monkeys receiving the dosage indicated.

(c) The human dosage (qd 1.5 day, mg/m<sup>2</sup>) indicated by an asterisk was used to obtain the animal: man ratio<sup>4</sup>.

(d) H. rat is the Holtzman line of Sprague-Dawley rat; F. rat is Fischer rat; S.D. is Sprague-Dawley rat.

(e) Average patient received one additional half dose on day 7. Maximum of 11 half doses given q.o.d.

(f) Average patient received four additional half doses q.o.d. Maximum of 11 half doses given q.o.d.

(g) Average patient received no additional therapy.

(h) Median duration of therapy to toxicity for daily treatment.

(i) Four additional half doses on days 7, 9, 11, and 13.

<sup>4</sup>Underlined values represent studies in which mg/m<sup>2</sup> was the original basis for dosage.

Table 2

A Comparison of Small-Animal LD<sub>10</sub>'s, Large-Animal Maximum Tolerated Doses, and Human Maximum Tolerated Doses on a Mg/Kg Basis

| Agent               | Mg/Kg (qd 1-5 Day Schedule)          |   |                           | MTD:<br>Rhesus<br>Monkey | MTD:<br>Dog | MTD:<br>Man |
|---------------------|--------------------------------------|---|---------------------------|--------------------------|-------------|-------------|
|                     | LD <sub>10</sub> :<br>Swiss<br>Mouse | LD <sub>10</sub> :<br>BDF <sub>1</sub><br>Mouse | LD <sub>10</sub> :<br>Rat |                          |             |             |
|                     |                                      |   |                           |                          |             |             |
| 1. Amethopterin     | 3.2                                  | 5.2   | 0.58                      | 3.0                      | 0.12        | 0.41        |
| 2. 6-Mercaptopurine | 86.0                                 | 62.0  | 51.0                      | 56.0                     | 22.0        | 27.0        |
| 3. 5-Fluorouracil   | 42.0                                 | 45.0  | 25.0                      | 18.0                     | 10.0        | 15.0        |
| 4. 5-FUDR           | 160.0                                | 190.0   | 89.0                      | 59.0                     | 40.0        | 30.0        |
| 5. Nitrogen Mustard | 1.3                                  | 0.90  | 0.37                      | 0.2                      | 0.48        | 0.2         |
| 6. Nitromin         | 45.0                                 | 31.0  | 7.10                      | 4.8                      | 4.4         | 2.0         |
| 7. L-Phenylalanine  | 5.1                                  | 5.5   | 2.3                       | 0.55                     | 0.63        | 0.2         |
| 8. Alanine Mustard  | 6.3                                  | 9.7   | -                         | 1.5                      | 1.5         | 0.9         |
| 9. Cytosan          | 93.0                                 | 110.0   | 12.0                      | 54.0                     | 12.0        | 10.0        |
| 10. Thiotepa        | 5.7                                  | 6.5   | 2.7                       | 1.0                      | 1.1         | 0.2         |
| 11. Myleran         | 15.0                                 | 15.0  | 3.7                       | 6.0                      | 6.0         | 0.7         |
| 12. BCNU            | 11.0                                 | 16.0  | 6.6                       | 5.3                      | 2.4         | 2.5         |
| 13. Actinomycin D   | 0.07                                 | 0.12  | 0.09                      | -                        | 0.03        | 0.015       |
| 14. Mitomycin C     | 2.3                                  | 2.2   | 1.3                       | 0.64                     | -           | 0.2         |
| 15. Vinblastin      | 0.60                                 | 0.53  | -                         | -                        | -           | 0.08        |
| 16. Vincristine     | 0.18                                 | 0.20  | -                         | -                        | -           | 0.024       |
| 17. Methyl GAG      | 59.0                                 | 93.0  | -                         | -                        | -           | 11.0        |
| 18. Hydroxyurea     | -                                    | -   | -                         | -                        | 560.0       | 160.0       |

Note: Average animal doses have been compared with human doses indicated by an asterisk in Table 1, and have been rounded to two significant figures.

Table 3

A Comparison of Small-Animal LD<sub>10</sub>'s, Large-Animal Maximum Tolerated

| Agent               | Doses and Human Maximum Tolerated Doses on a mg/m <sup>2</sup> Basis |   |   |                                     |                            |                          | Estimated<br>MTD<br>Man<br>(All Systems) |
|---------------------|--|---|---|-------------------------------------|----------------------------|--------------------------|--|
|                     | LD <sub>10</sub><br>Swiss<br>Mouse<br>(km=3)                         | LD <sub>10</sub><br>BDF <sub>1</sub><br>Mouse<br>(km=3) | LD <sub>10</sub><br>Hamster<br>(km=4.1) | LD <sub>10</sub><br>Rat<br>(km=5.2) | MID<br>Rhésus<br>(km=11.5) | MTD<br>Monkey<br>(km=19) |  |
| 1. Amethopterin     | 9.5  | 16.0  | 103.0                                   | 3.1                                 | 35.0                       | 2.0                      | 15.0                                     |
| 2. 6-Mercaptopurine | 257.0  | 186.0   | 320.0                                   | 266.0                               | 644.0                      | 434.0                    | 1000.0                                   |
| 3. 5-Fluorouracil   | 126.0  | 135.0   | 70.0                                    | 130.0                               | 207.0                      | 190.0                    | 555.0                                    |
| 4. 5-FUDR           | 494.0  | 574.0   | 165.0                                   | 463.0                               | 690.0                      | 760.0                    | 1110.0                                   |
| 5. Nitrogen Mustard | 3.8  | 2.6   | 5.3                                     | 1.9                                 | 2.3                        | 9.1                      | 7.4                                      |
| 6. Nitromin         | 135.0  | 94.0  | 37.0                                    | 55.0                                | 84.0                       | 74.0                     | 73.0                                     |
| 7. L-Phenylalanine  | 15.0   | 17.0  | 12.0                                    | 6.3                                 | 12.0                       | 7.4                      | 11.5                                     |
| Mustard             |  |   |   |                                     |                            |                          |  |
| 8. Alantine Mustard | 19.0   | 29.0  | 46.0                                    | 17.0                                | 29.0                       | 33.0                     | 22.8                                     |
| 9. Cytoxan          | 280.0  | 340.0   | 320.0                                   | 64.0                                | 621.0                      | 234.0                    | 370.0                                    |
| 10. ThioTEPA        | 17.0   | 20.0  | 42.0                                    | 16.0                                | 11.5                       | 21.0                     | 7.4                                      |
| 11. Myleran         | 45.0   | 45.0  |   | 19.0                                | 69.0                       | 114.0                    | 16.5                                     |
| 12. BCNU            | 34.0   | 47.0  | 48.0                                    | 34.0                                | 61.0                       | 45.0                     | 25.0                                     |
| 13. Actinomycin D   | 0.21   | 0.35  | 0.25                                    | 0.45                                | 0.57                       | 0.55                     | 0.34                                     |
| 14. Mitomycin C     | 6.9  | 6.5   | 7.0                                     | 6.5                                 | 7.4                        | 7.4                      | 6.9                                      |
| 15. Vinblastin      | 1.8  | 1.6   | 2.2                                     |                                     |                            |                          | 1.8                                      |
| 16. Vincristine     | 0.54   | 0.60  | 1.4                                     |                                     |                            |                          | 0.89                                     |
| 17. Methyl GAG      | 176.0  | 280.0   | 168.0                                   |                                     |                            |                          | 0.63                                     |
| 18. Hydroxyurea     |  |   |   |                                     |                            |                          | 211.0                                    |
|                     |  |   |   |                                     | 10,640.0                   | 420.0                    | 5900.0                                   |
|                     |  |   |   |                                     |                            |                          | -  |

Note: Average animal doses have been compared with human doses indicated by an asterisk in Table 1.  
 The last column is the weighted estimate from the animal results (See Appendix III).

Model (1) (Dose in man  $\text{mg}/\text{m}^2$ ) = 1 (Dose in animal system  $[\text{mg}/\text{m}^2]$ )

| <u>Animal System</u>       | <u>St. Deviation<br/>(log scale)</u> | <u>Multipliers for dose in animal system giving lower and upper standard deviation limits (<math>\text{mg}/\text{m}^2</math> scale)</u> |               |
|----------------------------|--------------------------------------|---|---------------|
|                            |                                      | <u>lower*</u>   | <u>upper*</u> |
| 1. monkey                  | .312                                 | .49   | 2.1           |
| 2. Swiss mouse             | .369                                 | .43   | 2.3           |
| 3. BDF <sub>1</sub> mouse  | .379                                 | .42   | 2.4           |
| 4. dog                     | .422                                 | .38   | 2.6           |
| 5. rat                     | .495                                 | .32   | 3.1           |
| 6. hamster                 | .601                                 | .25   | 4.0           |
| all combined<br>(weighted) | .299                                 | .50   | 2.0           |

Model (2) (Dose in man  $\text{mg}/\text{m}^2$ ) =  $A_i$  (Dose in animal system  $[\text{mg}/\text{m}^2]$ )

| <u>Animal System</u>       | <u>Estimate<br/>of<br/><math>A_i</math></u> | <u><math>A_i + 2 \text{ S.E.}</math></u> | <u>St. Deviation<br/>(log scale)</u> | <u>Multipliers for dose in animal system giving lower and upper st. deviation limits (<math>\text{mg}/\text{m}^2</math> scale)</u> |              |
|----------------------------|---|--|--------------------------------------|--|--------------|
|                            |   |  |                                      | <u>lower</u>   | <u>upper</u> |
| 1. monkey                  | 1.15  | .79 - 1.67                               | .293                                 | .51  | 2.0          |
| 2. Swiss mouse             | 1.39  | .93 - 2.06                               | .323                                 | .48  | 2.1          |
| 3. rat                     | 2.08  | 1.35 - 3.21                              | .339                                 | .46  | 2.2          |
| 4. BDF <sub>1</sub> mouse  | 1.29  | .84 - 1.97                               | .346                                 | .45  | 2.2          |
| 5. dog                     | 1.05  | .60 - 1.83                               | .400                                 | .40  | 2.5          |
| 6. hamster                 | 1.32  | .61 - 2.86                               | .556                                 | .28  | 3.6          |
| all combined<br>(weighted) | 1.36  | 1.13 - 1.60                              | .275                                 | .53  | 1.9          |

\*As an example, the toxic dosage of amethopterin in the monkey is  $40.2 \text{ mg./m}^2$ . Thus, the predicted MTD in man is  $40.2 \text{ mg./m}^2$  with one st. deviation limits  $40.2 \times .49 = 19.7 \text{ mg./m}^2$  to  $40.2 \times 2.1 = 84.4 \text{ mg./m}^2$ .

Table 5

Predicted Dosages (mg/m<sup>2</sup>) in Man Using Each Animal System  
and All Systems Combined

| Agent               | Swiss | BDF   | Overall |       |        |       | Man        |          |
|---------------------|-------|-------|---------|-------|--------|-------|------------|----------|
|                     | Mice  | Mice  | Hamster | Rat   | Monkey | Dog   | Unweighted | Weighted |
| 1. Amethopterin     | 13.2  | 20.6  | 116.0   | 6.4   | 40.2   | 2.5   | 17.0       | 15.7     |
| 2. 6-Mercaptopurine | 357.0 | 240.0 | 424.0   | 554.0 | 740.0  | 457.0 | 435.0      | 444.0    |
| 3. 5-Fluorouracil   | 244.0 | 174.0 | 92.7    | 271.0 | 238.0  | 200.0 | 182.0      | 210.0    |
| 4. 5-FUDR           | 686.0 | 740.0 | 219.0   | 964.0 | 793.0  | 800.0 | 581.0      | 699.0    |
| 5. Nitrogen Mustard | 5.3   | 3.4   | 7.0     | 4.0   | 2.6    | 9.6   | 4.8        | 4.2      |
| 6. Nitroimin        | 187.0 | 121.0 |         | 77.0  | 63.1   | 88.3  | 99.1       | 99.6     |
| 7. L-Phenylalanine  | 20.8  | 21.9  |         | 25.0  | 7.2    | 12.6  | 16.0       | 15.6     |
| 8. Alanine Mustard  | 26.4  | 37.3  | 61.0    |       | 19.5   | 30.5  | 35.3       | 31.0     |
| 9. Cytokan          | 388.0 | 439.0 | 424.0   | 133.0 | 711.0  | 246.0 | 345.0      | 362.0    |
| 10. Thioplepa       | 23.6  | 25.8  | 55.6    | 29.1  | 13.2   | 22.1  | 25.7       | 22.5     |
| 11. Myleran         | 62.4  | 58.0  |         | 39.5  | 79.3   | 120.0 | 66.8       | 64.6     |
| 12. BCNU            | 47.2  | 60.5  | 63.5    | 70.8  | 68.4   | 47.3  | 59.1       | 59.6     |
| 13. Actinomycin D   | 0.29  | 0.27  | 0.33    | 0.44  |        | 0.54  | 0.46       | 0.46     |
| 14. Mitomycin C     | 9.6   | 8.4   | 9.3     | 13.5  | 8.5    |       | 9.2        | 9.3      |
| 15. Vinblastin      | 2.5   | 2.1   | 2.9     |       |        |       | 2.4        | 3.0      |
| 16. Vincristine     | 0.75  | 0.77  | 1.9     |       |        |       | 0.85       | 0.85     |
| 17. Methyl GAG      | 244.0 | 361.0 | 222.0   |       |        |       | 287.0      | 420.0    |
| 18. Hydroxyurea     |       |       |         |       |        |       |            | 5900.0   |
|                     |       |       |         |       |        |       | 11,190.0   |          |

## More Detailed Description of the Toxicologic Data Used

*Small animals (mouse, rat, and hamster).*—The classic end point for assessing drug toxicity to small animals is death (LD10, LD50, LD90). A reliable method of determining the lethality of a drug is to give an appropriately spaced series of doses to groups of about 10 animals each; to record percent deaths at each drug level; and then to plot the dose-mortality data on log-probit paper (7), draw a line of best fit, and read the lethal dose for 10, 50, or 90%, or any other fraction of the animals. The reliability of such end points depends on the number of animals, and the LD10, LD50, or LD90 (in mg/kg or mg/m<sup>3</sup>) for a given animal species is incomplete unless it is accompanied by information on the route of administration, the dosage schedule, and the period of observation for delayed death after cessation of drug administration. Useful information may be gained from the median day of death, during and after administration of various dose levels, and the slope of the dose-mortality curve.

Most of the mouse toxicity data in this analysis were obtained by Schmidt (7) and Griswold et al. (3); the rat toxicity data by Schmidt (7); and the hamster toxicity data by Griswold et al. (8). All toxicity data were plotted as indicated previously and values were read from lines of best fit. About 50 to more than 100 animals were used in each toxicity determination. The ip route was used in most instances, and all animals were kept for 1-3 weeks after the end of treatment for observation of delayed death. The schedules used most frequently were qd 1-5, qd 1-7, qd 1-11, and qd 1-15 days.

We are aware that the LD10 is not as reliable statistically as the LD50; however the LD10 is closer to the maximum doses accepted in typical experimental cancer chemotherapy trials and to the maximum doses reached in clinical drug evaluation.

Some indication of the overall reproducibility and reliability of LD10's obtained by the general procedure described may be found in calculations by Griswold et al. (3): "among the 219 LD10's determined (Swiss mice, qd 1-7; BDF, mice, qd 1-7 and qd 1-11 days), the median range between the lower and upper 95% confidence limits was 0.35 logs." No con-

clusion can be drawn as to the reliability of a LD10 obtained by this method.

The procedures for obtaining and interpreting toxicity data for the rat and hamster were essentially the same as those described for mouse.

*Large animals (dog and monkey).*—Since it is rarely feasible to obtain extensive dose-mortality data for dogs and monkeys, accurate LD10's, LD50's, or LD90's usually are not available. However the lethal dose range for such species is determined for anticancer agents being considered for clinical trial. In general the dose-mortality data for dogs and monkeys consisted of daily dose levels (2-fold increases) given to groups of 2-4 animals until 100% mortality. The approximate toxicologic end point selected for this analysis was the highest dose which killed 0% of 2-4 animals. Usually, doubling this dose killed all the animals. As with other species, the dose levels given to dogs and monkeys were corrected to a schedule of qd 1-5 days.

The major limiting toxic effects of the various classes of agents considered in this analysis were marrow depression and gastrointestinal lesions. Table 1 (Appendix I) presents the basis for rating the intensity of these dose-related hematopoietic effects and gastrointestinal and soft tissue lesions.

*Man.*—Most clinical cancer chemotherapy studies use an experimental design in which the drug dose and schedule are varied so that each patient receives the optimum dose of agent and therefore each patient becomes the unit of study. For this type of study, a detailed analysis of the toxic effect of a certain drug, dose, schedule, and route of administration becomes very difficult. For this reason the published literature and unpublished data available were searched for studies using a fixed-dose schedule and fixed route of administration for a series of patients, followed by a period of observation without chemotherapy. In such circumstances it was possible to assess the effects of treatment on the individual. When possible, studies were chosen of patients who had normal peripheral blood and bone marrow and who had not received marrow-suppressive therapy within the 6 weeks preceding the study. Another criterion for selecting data was that objective toxic effects were observed in a significant

Table 1. Appendix I

Rating of the Intensity of the Major Toxicologic Reactions as Observed in Dogs and Monkeys<sup>a</sup>

| Classification        | Reaction                   | Determined By    | Basis for Rating as:                           |  |                          |
|-----------------------|----------------------------|------------------|--|--|--------------------------|
|                       |                            |                  | 0  | Mild (or +)                                      | Moderate (or ++)         |
| Anemia*               | Decrease in RBC count      | Essentially none | 1.0-1.5 $\times 10^6$ /cmm < control           | < 4.5 to > 3.5 $\times 10^6$ /cmm                | < 3.5 $\times 10^6$ /cmm |
| Neutropenia*          | Decrease in relic-% RBC    | Essentially none | > 0.5%; < 1/2 control                          | > 0.01%; < 0.05%                                 | < 0.01%                  |
| Hemoconcentration*    | Increase in hematocrit     | Essentially none | > 10%; < 20% control                           | > 20%; < 40% control                             | > 30% control            |
| Leucopenia*           | Decrease in WBC count      | Essentially none | < 1/2 control                                  | > 2.5 $\times 10^3$ /cmm; < 5 $\times 10^3$ /cmm | < 2.5 $\times 10^3$ /cmm |
| Thrombocytopenia*     | Decrease in platelet count | Essentially none | > 10% cmm; < 1/2 control                       | > 10% cmm; < 10% cmm                             | < 10% cmm                |
| Marrow depression*    | Decrease in absolute count | Essentially none | > 10 <sup>3</sup> /cmm; < 5 $\times 10^3$ /cmm | > 5 $\times 10^3$ /cmm; < 10 <sup>3</sup> /cmm   | < 5 $\times 10^3$ /cmm   |
| Hemorrhagic lesions** | GI tract                   | Essentially none | Isolated, punctate                             | Gross - limited area                             | Gross - widespread       |
| Hemorrhagic lesions** | Generalized, soft tissue   | Essentially none | Isolated, punctate                             | Gross - limited area                             | Gross - widespread       |
| CNS stimulation       | Convulsions                | Essentially none | Described as observed                          | Described as observed                            | Described as observed    |
| Other                 | ...                        | Essentially none | Unspecified as observed                        | Unspecified as observed                          | Unspecified as observed  |

Note: \*Grouped under the term "marrow depression" (MD) in this general paper.

\*\*Grouped under the term "gastrointestinal tract damage" (GI) in this paper.

Detailed data regarding specific hematologic and tissue and organ damage are available but are not included herein. In Table 1 of the text, only the average degree of marrow depression and gastrointestinal damage are presented under 0, mild, moderate, or severe.

number of patients treated with a certain dose and schedule. The most commonly used parameter was white blood cell count (WBC). The toxic manifestations were then graded on a 0 to 3+ scale, i.e. none, mild, moderate, or severe (when possible). Chemotherapy experiments which used very small doses of drug given in periods of 6-8 weeks were not included because of the lack of an appropriate counterpart in experimental systems. Therefore we tried to find tests in which maximum tolerated doses were given in minimum time intervals by fixed-dose schedules (and fixed routes).

#### APPENDIX II

##### Relationship Between Drug Doses in Milligram Per Kilogram and in Milligram Per Square Meter of Surface Area for Man and for Small and Large Animals

In table 1 (Appendix II) the estimated square meters of surface area are given for several body weights (kg) within each mammalian species. The surface area in square meters was estimated by the formula

$$(\text{body surface area}) = \frac{K \times w^{0.7}}{10^4}$$

The  $K$  values are given for each species by Spector (ref. 40, p 175) and  $w$  is body weight in grams. The  $K$  values differ among species

so within species; however a single factor was chosen for each species except man. The conversion factors ( $km$ ) were obtained simply by dividing the body weight by surface area. Thus to convert a dose in mg/kg to a dose in mg/m<sup>2</sup>, we use the approximate formula

$$(\text{dose in mg/m}^2) = (km) \times (\text{dose in mg/kg})$$

where the ( $km$ ) factor is selected according to the species and body weight. For example, a dose of 20 mg/kg/day given to a 20-g mouse is approximately equal to  $20 \times 3 = 60$  mg/m<sup>2</sup>/day.

Note that the ( $km$ ) factor is simply

$$(km) = \frac{10^4 \times (\text{kg})^{0.7}}{K}$$

where kg is weight in kilograms. The ( $km$ ) factors used in this study were

| Species | Approx. wt. (kg) | (km) factor |
|---------|------------------|-------------|
| Man     | 60               | 37          |
| Mouse   | .020             | 3.0         |
| Rat     | .100             | 5.2*        |
| Hamster | .050             | 4.1*        |
| Monkey  | 2.5              | 11.5        |
| Dog     | 7.0-8.0          | 19.0-1      |

\* Except as otherwise indicated in table 1 of ter-

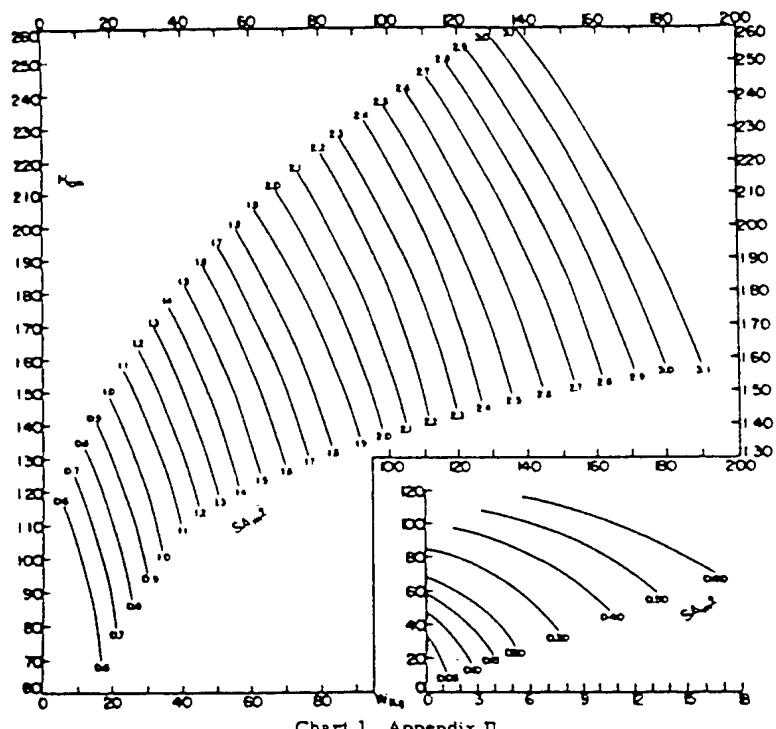


Chart 1. Appendix II

Diagram for Determination of Human Surface Area from Height and Weight.  
(Insert is Used for Low Range of  $S_Am^2$  from 0.05 to 0.80). Taken from  
Sendroy and Cecchini, J. Applied Physiol. 7: 1-12 (1954).  $H_{cm}$  = height in  
centimeters;  $W_{kg}$  = weight in kilograms;  $S_Am^2$  = surface area in sq. meters.

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Table I. Appendix II

Conversion Factors (Dosages in mg./kg to mg./m<sup>2</sup>) for the MouseRat, Monkey, Dog and Man Given Body Weight Only.

| <u>Species</u> | <u>K</u> | <u>Body Wt.<br/>(kg)</u> | <u>Square Meters<br/>Area</u> | <u>Conversion<br/>Factor (km)</u> |
|----------------|----------|--------------------------|-------------------------------|-----------------------------------|
| Mouse          | 9.0      | 0.018                    | 0.0062                        | 2.9                               |
|                |          | 0.020                    | 0.0066                        | 3.0                               |
|                |          | 0.022                    | 0.0071                        | 3.1                               |
|                |          | 0.024                    | 0.0075                        | 3.2                               |
| Rat            | 9.0      | .050                     | 0.0122                        | 4.1                               |
|                |          | .070                     | 0.0153                        | 4.6                               |
|                |          | .080                     | 0.0167                        | 4.8                               |
|                |          | 0.100                    | 0.0194                        | 5.2                               |
|                |          | 0.150                    | 0.0254                        | 5.9                               |
|                |          | 0.200                    | 0.0308                        | 6.5                               |
|                |          | 0.250                    | 0.0357                        | 7.0                               |
| Monkey         | 11.8     | 2.0                      | 0.188                         | 10.5                              |
|                |          | 2.5                      | 0.217                         | 11.5                              |
|                |          | 3.0                      | 0.244                         | 12.3                              |
| Dog            | 10.1     | 6.0                      | 0.334                         | 18.0                              |
|                |          | 7.0                      | 0.369                         | 19.0                              |
|                |          | 8.0                      | 0.404                         | 19.8                              |
|                |          | 9.0                      | 0.437                         | 20.6                              |
| Man (avg.)     |          | 5.0                      | 0.26                          | 19.0                              |
|                |          | 10.0                     | 0.44                          | 23.0                              |
|                |          | 20.0                     | 0.80                          | 25.0                              |
|                |          | 40.0                     | 1.30                          | 31.0                              |
|                |          | 60.0                     | 1.62                          | 37.0                              |
|                |          | 70.0                     | 1.80                          | 39.0                              |
|                |          | 80.0                     | 1.96                          | 41.0                              |

Table 2, Appendix II

Conversion Factors (Dosages in Mg/Kg to Mg/M<sup>2</sup> Body Surface Area) for Man Given Height and Body Weight

| Body Wt.<br>Kg.<br>Pounds | Foot:<br>Inches:<br>Cm. | Height |       |       |       |       |       |       |       |       |     |
|---------------------------|-------------------------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-----|
|                           |                         | 1.3    | 1.7   | 2.0   | 2.3   | 2.7   | 3.0   | 3.3   | 3.6   | 3.9   | 4.3 |
| 6 11                      | 16 20<br>40 50          | 22 19  | 17 15 | 15 14 |       |       |       |       |       |       |     |
| 10 22                     | 26 30<br>50 60          | 26 24  | 23 21 | 19 18 |       |       |       |       |       |       |     |
| 15 33                     |                         | 26 25  | 24 22 | 21 19 | 18    |       |       |       |       |       |     |
| 20 44                     |                         | 29 28  | 26 25 | 24 22 | 21    |       |       |       |       |       |     |
| 25 55                     |                         |        | 30 28 | 27 26 | 24 23 | 22    |       |       |       |       |     |
| 30 66                     |                         |        | 33 31 | 30 29 | 27 26 | 25    |       |       |       |       |     |
| 35 77                     |                         |        | 34 32 | 31 30 | 28 27 | 26    |       |       |       |       |     |
| 40 88                     |                         |        | 35 33 | 32 31 | 30 29 | 28    | 27    |       |       |       |     |
| 45 99                     |                         |        | 37 35 | 34 33 | 31 30 | 29    | 28    |       |       |       |     |
| 50 110                    |                         |        | 38 37 | 36 35 | 34 33 | 31 30 | 29    |       |       |       |     |
| 55 121                    |                         |        | 39 38 | 37 35 | 34 33 | 31 30 | 29    |       |       |       |     |
| 60 132                    |                         |        | 41 39 | 38 37 | 36 35 | 34 33 | 32 31 |       |       |       |     |
| 65 143                    |                         |        |       | 41 40 | 39 38 | 36 35 | 34 33 | 32 31 |       |       |     |
| 70 154                    |                         |        |       | 42 41 | 40 39 | 37 36 | 35 34 | 33 32 | 31    |       |     |
| 75 165                    |                         |        |       | 44 43 | 41 40 | 39 38 | 37 36 | 35 34 | 33 32 | 31    |     |
| 80 176                    |                         |        |       | 45 44 | 43 42 | 41    | 40 39 | 38 37 | 36 35 | 34    |     |
| 85 187                    |                         |        |       | 45 44 | 43 42 | 41    | 40 39 | 38 37 | 36 35 | 34    |     |
| 90 198                    |                         |        |       |       | 45 44 | 43 42 | 41    | 40 39 | 38 37 | 36 35 | 34  |
| 95 209                    |                         |        |       |       |       | 46 45 | 44 43 | 42 41 | 40 39 | 38 37 |     |
| 100 220                   |                         |        |       |       |       |       | 46 45 | 44 43 | 42 41 | 40 39 |     |
| 105 231                   |                         |        |       |       |       |       |       | 47 46 | 45 44 | 43    |     |
| 110 242                   |                         |        |       |       |       |       |       |       | 48 47 | 46 45 | 43  |

Note: The underlined conversion factors are for individuals of approximately average height to body weight ratios.

The above km factors were calculated from data presented in: Spector, W. S., Handbook of Biological Data, W. B. Saunders Company, Philadelphia and London (1958). The basic data (Spector) were derived according to the method of Sendroy and Cecchini, 1954 (Sendroy, J., Jr., and Cecchini, L. P., J. Applied Physiology 7: 1-12, 1954).

Example: A dosage of 2.5 mg/kg/day of 6-MP (to a 20-kg child of 110-cm height) is equal to  $2.5 \times 25$  (km factor) • 62.5 mg/m<sup>2</sup>/day.

Table A (Appendix II) presents the (km) factors for man. Chart 1 (Appendix II) is a diagram for determining the surface area of humans from height and weight (taken from Sendroy and Cecchini [39]).

It may be of some interest to indicate how the results of the analysis would have changed if surface area had been estimated as

$$(\text{surface area}) = (\text{kg})^{\frac{2}{3}}.$$

The rationale is that since body surface area is clearly not the target area of action of the drug but presumably is proportional to the true target area, it is sufficient to measure surface area in units proportional to the true target area. The surface area unit is simply the two-thirds power of weight, though it is not easy to visualize this quantity. This leads to the formula

$$(\text{dose in mg/surface area}) = (\text{km}) \times (\text{dose in mg/kg})$$

where  $(\text{km}) = (\text{kg})^{\frac{2}{3}}$  instead of  $[(\text{kg})^{\frac{2}{3}} \times 10^3]/K$  as before. If the  $K$  factors were the same for each species, the analysis in the new surface area unit would be exactly the same as that given. Since the  $K$  factors do differ among species, ranging from 9.0-11.8, the results of a re-analysis would differ slightly from those given here but certainly not substantially. The most appropriate  $K$  factor for any drug would be that which makes the two-thirds power of weight for each species equal to the surface area where the drug acts. Since this information is not generally known, it matters little whether the  $K$  factors among species are assumed to be the same or to differ slightly.

### APPENDIX III

#### Statistical Considerations

The notation used is as follows:

$y$  = true log (dose in  $\text{mg}/\text{m}^2$ ) in man

$x_i$  = true log (dose in  $\text{mg}/\text{m}^2$ ) in animal system  $i$ , ( $i = 1, \dots, 6$ ).

The doses are the MTD in man and the LD<sub>10</sub> in each animal system. Now,  $y$  and  $x_i$  are variables that have particular values when a drug is given according to a certain schedule and route of administration (assumed here to be qd 1-5 days and the ip or iv route with a

exception). Because of random error, and other factors, we do not observe  $y$  and  $x_i$ , but

$$y' = y - d_i \quad (A1)$$

$$x'_i = x_i + e_i \quad (A2)$$

where  $d_i$  and  $e_i$  are random variables. We assume that  $d_i$  and  $e_i$  are independently distributed with zero means and are independent of  $y$  and  $x_i$ . The primes indicate observed values

We postulate that the underlying structural relationship (model) is

$$y = a_i + x_i, \quad (i = 1, \dots, 6) \quad (A3)$$

where  $a_i = \log A_i$  according to the notation in the text. In model (1),  $a_i$  is zero and in model (2) it is a parameter to be estimated. These are the simplest models that could be considered. Actually the more general relationship  $y = a_i + \beta_i x_i$  was also considered but since the estimates of  $\beta_i$  ( $i = 1, \dots, 6$ ) were all near 1, only the simpler models given were investigated further.

Substituting (A1) and (A2) into (A3), we have

$$y' - d_i = a_i + x'_i - e_i$$

$$y' = a_i + x'_i + (d_i - e_i)$$

where  $(d_i - e_i)$  is a random variable with zero mean. We have  $n$  pairs (usually 17) of observations,  $(y'_j, x'_{ij})$ ,  $j = 1, \dots, n$ , and we want to estimate the parameter  $a_i$  in model (1). Since each animal system provides an estimate of  $y$ , we will also be interested in a combined estimate of  $y$ .

The aim in estimating the parameter of the model is to predict a value of  $y$  (denoted by  $\hat{y}$ ) for a given value of  $x'$ . The prediction equation is

$$\hat{y} = \hat{a}_i + x'_i \quad (A4)$$

As Lindley (38) noted,  $x'_i$  is measured with error and standard least squares may be used for estimating  $a_i$ . Thus the estimate of  $a_i$ , denoted by  $\hat{a}_i$ , is simply

$$\hat{a}_i = \frac{\sum (y'_j - x'_{ij})}{n}, \quad (i = 1, 2, \dots, 6)$$

The values of  $A_i$  given in the text are antilogs of  $\hat{a}_i$ .

To obtain an estimate based on results from all animal systems, we can simply average the values of  $\hat{y}$  from the six animal systems or calculate a weighted average where the weight for each  $y$  is inversely proportional to its variance. The weighted combined estimate is

$$\hat{y}_{ws} = \frac{\sum_{i=1}^6 w_i (\hat{a}_i + x_i)}{\sum_{i=1}^6 w_i}$$

where

$$w_i = \frac{1/s_i^2}{\sum_{i=1}^6 1/s_i^2}$$

and  $s_i^2$  is the variability about  $\hat{y}_i$ . That is,

$$s_i^2 = \frac{\sum_{i=1}^6 (y_i - \hat{y}_i)^2}{n_i - 1}, \quad (i = 1, \dots, 6)$$

for model (2). For model (1) the divisor is  $n$ .

A sample of the calculations required is given for illustrative purposes, assuming that only two drugs, amethopterin and 6-mercaptopurine (6-MP), have been studied in Swiss mice and man. The data are in log (dose in  $\text{mg}/\text{m}^2$ ):

| Drug         | Man ( $\hat{y}_i$ ) | Swiss mice ( $x_i$ ) |
|--------------|---------------------|----------------------|
| Amethopterin | 1.176               | 0.978                |
| 6-MP         | 3.000               | 2.410                |

For model (1) the predicted values of the dose in man are simply the doses observed in Swiss mice, namely, 9.5  $\text{mg}/\text{m}^2$  for amethopterin and 257.0  $\text{mg}/\text{m}^2$  for 6-MP. The standard deviation is

$$s_i = \sqrt{\frac{(1.176 - 0.978)^2 + (3.00 - 2.410)^2}{2}} = 0.440.$$

For model (2) we have

$$\hat{a}_i = \frac{\sum y_i - \sum x_i}{2} = \frac{4.176 - 3.388}{2} = 0.394$$

and so  $\hat{A} = 2.48$ . The predicted values of  $\hat{y}$  in man are

| Drug         | Equation                            | Dose ( $\text{mg}/\text{m}^2$ ) |
|--------------|-------------------------------------|---------------------------------|
| Amethopterin | $\hat{y}_i = 0.394 + .978 = 1.372$  | 23.6                            |
| 6-MP         | $\hat{y}_i = 0.394 + 2.410 = 2.804$ | 636.8                           |

The standard deviation for model (2) is:

$$s_i = \sqrt{\frac{(1.372 - 1.176)^2 + (3.000 - 2.804)^2}{1}} = 0.277$$

and  $1/s_i^2$  is the term in the numerator and the first term in the denominator of  $w_i$ . The standard error of  $a$  is

$$\text{SE of } a = \frac{0.277}{\sqrt{2}} = 0.196.$$

#### LIST OF COMPOUNDS

- Actinomycin D: NSC-3053.
- Alanine mustard: NSC-17663; DL-alanine, *N,N*-bis(2-chloroethyl)-, hydrochloride.
- Amethopterin: NSC-740; glutamic acid, *N*-[*p*-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-.
- BCNU: NSC-409962; urea, 1,3-bis(2-chloroethyl)-1-nitroso-.
- Cytoxan: NSC-26271; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, hydrate.
- 5-Fluorouracil: NSC-19893.
- 5-FUDR: NSC-27640; uridine, 2'-deoxy-5-fluoro-.
- Hydroxyurea: NSC-32065.
- 6-Mercaptopurine: NSC-755; purine-6-thiol, hydrate.
- Methyl-GAG: NSC-32946; guanidine, 1,1'-(methylene-thanediylidine)dinitroldi-, dihydrochloride, hydrate.
- Mitomycin C: NSC-26980; carbamic acid, ester with 6-amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-5-methylazirino[2',3':3,4]pyrrolo[1,2-*a*]-indole-4,7-dione.
- Myleran: NSC-750; 1,4-butanediol, dimethanesulfonate.
- Nitrogen mustard (HN2): NSC-762; diethylamine, 2,2-dichloro-*N*-methyl-, hydrochloride.
- Nitromin: NSC-10107; diethylamine, 2,2-dichloro-*N*-methyl-, *N*-oxide, compd. with hydrochloride (1:1).
- L-Phenylalanine mustard: NSC-8806; L-alanine, 3-[*p*-[bis(2-chloroethyl)amino]phenyl]-, hydrochloride.
- ThioTEPA: NSC-6396; phosphine sulfide, tris(1-aziridinyl)-.
- Vinblastine: NSC-49842; vincleukoblastine, sulfate, hydrate.
- Vincristine: NSC-67574; leurocristine, sulfate.

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